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Inflation pressures and times during initial resuscitation of preterm infants

Short running title: Resuscitation of preterm infants

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ABSTRACT

Background: The optimal combination of inflation pressures and times to produce adequate expiratory tidal volumes during initial resuscitation in prematurely born infants has not been determined. Our aim was to assess combinations of inflation pressures and times and the resulting expiratory tidal volume levels using a respiratory function monitor.

Methods: Sixty-four infants born before 34 weeks of gestation were studied. The infants were divided according to whether the inflation pressures (PIP-PEEP) were less than or ≥ 20 cm H₂O during the first five inflations delivered by a face mask and those groups were subdivided according to whether the inflation times were less than or ≥ 1.5 seconds.

Results: Inflation pressures of ≥ 20 cm H₂O compared to lower pressures at both inflation times produced significantly higher expiratory tidal volumes. Longer compared to shorter inflation times when the inflation pressure was ≥ 20 cm H₂O resulted in no significant difference in expiratory tidal volumes. At < 20 cm H₂O inflation pressure, longer inflation times overall resulted in higher end tidal volumes, but the majority of infants had a tidal volume less than the anatomical dead space.

Conclusions: At higher inflation pressures, a longer inflation time was not necessary to increase expiratory tidal volumes.

Key words: face mask; intubation; preterm infant; resuscitation; tidal volumes

INTRODUCTION

In recent years, there has been increasing interest in the use of sustained inflation pressures (15-20 seconds) during the resuscitation of preterm infants. The results of studies of sustained inflations in animal models, however, have yielded conflicting results. One study in preterm lambs showed no benefit using that technique [1], whereas another demonstrated that ventilation with an initial 30 seconds sustained inflation resulted in more rapidly increasing cerebral blood flow in asphyxiated near term lambs, but was associated with greater disruption of blood brain barrier function [2]. In contrast, in premature rabbits, 10 and 20 seconds sustained inflations increased the inspiratory volume and produced a greater functional residual capacity and a 20 second inflation more uniformly aerated the lung before ventilation was started [3]. In newborn infants, one study found that sustained inflations reduced the need for subsequent intubation, the use of surfactant and the incidence of bronchopulmonary dysplasia (BPD) [4]. The authors, however, compared sustained inflation with positive end expiratory pressure (PEEP) using a t-piece to generate positive pressure inflations using a self-inflating bag which may not have provided adequate PEEP [4]. Hence, the positive results may reflect use of a sustained inflation and/or adequate PEEP [4]. A systematic review comparing sustained inflation to positive pressure ventilation reported no improvements in BPD or death, although there was a reduced requirement for subsequent mechanical ventilation [5]. The authors [5] recommended that sustained inflations during resuscitation should be limited to randomised trials until further studies demonstrated efficacy and safety. A study published after the systematic review [5] found a non significant ($p=0.06$) increase in the incidence of pneumothorax

using sustained inflations [6]. A recent meta-analysis of two trials highlighted that an initial sustained (15 seconds) lung inflation compared to inflations \leq one second was not associated with significant reductions in mortality or chronic lung disease [7].

Currently, the United Kingdom Resuscitation Council recommends that during each of the initial five inflations delivered via a face mask, a peak inflation pressure of 20-25 cm H₂O which is sustained over two to three seconds should be used [8]. Those recommendations, however, are based on the results of studies of the resuscitation of term born infants indicating that a peak inflation pressure of 25–30 cm H₂O led to tidal volumes of less than 5 ml/kg [9]. In addition, a functional residual capacity (FRC) was rarely formed before the infant made spontaneous breaths in association with lung inflations [9]. Furthermore, inspection of the tidal volume traces indicated that, although the inspiratory pressure plateau had been maintained for up to one second, the tidal volume had not reached equilibrium [9]. When, however, a peak inflation pressure of 30 cm H₂O was maintained for up to five seconds for the first inflation, the tidal volumes and FRCs generated were similar to those found in spontaneously breathing, term infants [9]. In 2010 [10] the International Liaison Committee advised that the risk and benefits of using a peak pressure of 20-25 cm H₂O sustained for two to three seconds for the first five inflations had not been evaluated.

Using respiratory function monitoring, we have demonstrated that during the resuscitation of prematurely born infants, the first five inflations were rarely

maintained for more than one second, although those performing resuscitation had received appropriate training [11]. We also demonstrated a significant positive correlation between expired tidal volumes and inflation pressures, but not inflation times [11]. Furthermore, we found no significant relationship between the inflation time and the inflation flow time [12]. Whether, however a long inflation time with a high inflation pressure might be more effective has not been determined. Our aim, therefore, was to, using a respiratory function monitor, to assess different combinations of inflation pressures and times during initial face mask resuscitation to determine which resulted in the greatest expiratory tidal volumes.

METHODS

Infants born at less than 34 weeks of gestational age requiring resuscitation at birth at King's College Hospital NHS Foundation Trust, London, UK, were eligible for entry into this observational study unless they had major congenital anomalies. We included infants born at or less than 34 weeks of gestational age as such infants are more likely to require resuscitation compared to infants born at a higher gestational age. Ethical approval was granted by the Outer North London Research Ethics Committee who required parental written consent only for analysis of the data, which was obtained when the mother was on the postnatal ward.

Resuscitation protocol

The clinicians involved in the resuscitations had all been trained in newborn life support and had received the Resuscitation Council, UK NLS provider certificates. All had completed at least 12 months training on a tertiary level neonatal unit. During resuscitation the respiratory function monitor was set to display flow, expiratory tidal volume and airway pressure. Positive pressure inflations were generated by a t-piece device (Neopuff Infant resuscitator, Fisher & Paykel Healthcare, Auckland, New Zealand) attached to the face mask. The Neopuff, a continuous flow, pressure-limiting device, had a built in manometer, a positive end expiratory pressure (PEEP) valve and a gas flow rate of 5 l/minute. The safety pressure relief valve was set at 30 cm H₂O. The clinicians were advised to follow current recommendations by the UKRC, that is, to use a peak inflation pressure of 20-25 cm H₂O with a PEEP level of 4-5 cm H₂O and to maintain the first five inflations for two to three seconds [8, 10]. The peak inflation pressure was to be increased if chest wall expansion was thought inadequate. All infants were initially resuscitated with an inspired fraction of oxygen (FiO₂) of 0.21. The t-piece was attached to a round face mask (Marshall Infant, Bath, UK). A size 0 or 1 mask was selected by the clinician according to which mask size they felt would be most likely to achieve an adequate seal. Oxygen saturation monitoring was routinely used.

Monitoring equipment

The respiratory function monitor used [12, 13] was an NM3 respiratory profile monitor (RPM) (Philips Respironics, Conneticut, USA). The monitor was assessed using water manometers and found to give accurate pressure

measurements, which were linear across the pressure range. The monitor was connected to a Laptop (Dell Latitude, Dell, Bracknell, UK) with customised Spectra software (3.0.1.4) (Grove Medical, London, UK). The NM3 respiratory profile monitor had a combined pressure, flow and carbon dioxide (CO₂) sensor and this was placed in line between the t-piece and the face mask. The flow and pressure measurements were made via a fixed orifice differential pressure pneumotachograph. Respired gas flowing through the flow sensor caused a small pressure drop across the two tubes connected to the sensor. The pressure drop was transmitted through the tubing to a differential pressure transducer located inside the monitor. One of the tubes was also connected to a second pressure transducer to measure the airway pressure. The NMS monitor is automatically calibrated for flow and pressure according to the factory-stored calibration in the monitor. According to the manufacturer's information, the accuracy of the flow sensor was $\pm 3\%$ and the airway pressure was $\pm 2\%$. The accuracy of the pneumotachograph was confirmed using a calibration syringe. Clinical outcomes were obtained from the medical notes. These included the proportion of infants in each group who required mechanical ventilation, the duration of initial ventilation, the total duration of ventilation, the duration of oxygen dependency and the proportion in each group who developed bronchopulmonary dysplasia (diagnosed as oxygen dependency at 28 days).

ANALYSIS

Resuscitation groups

The infants were not randomised, but were retrospectively assigned to one of four groups according to the inflation pressure (peak inflation pressure-PEEP)

and inflation times they received during the first five inflations during resuscitation by face mask. The four groups were:

- < 20 cmH₂O with short inflation times (< 1.5 seconds)
- < 20 cmH₂O with long inflation times (≥ 1.5 seconds)
- ≥ 20 cmH₂O with short inflation times (< 1.5 seconds)
- ≥ 20 cmH₂O with long inflation times (> 1.5 seconds)

(< 20 cm H₂O lower inflation pressures; ≥ 20 cm H₂O higher inflation pressures). An inflation time < 1.5 seconds or ≥ 1.5 seconds was used as 1.5 seconds was the median duration of inflation in the study group.

Infants who could be matched in each group for gestational age (\pm one week) were included in the analysis, unless they had made an inspiratory effort immediately after birth and before the start of resuscitation. We determined by assessment of the flow, volume and pressure traces if an infant had generated an inspiratory effort during inflation (an active inflation) and such inflations were excluded from the analysis. From the first five passive inflations, the following were analysed: the peak inflating (PIP) and positive end expiratory pressure (PEEP), the inflation pressure, the expiratory tidal volumes (Tve) and face mask leak. The size of the leak was expressed as the difference between the expiratory and inspiratory volumes as a percentage of the inspiratory volume.

Statistical analysis

The data were not normally distributed, hence differences across the four groups were assessed for statistical significance using the Kruskal-Wallis test and differences between groups assessed for statistical significance using the Mann Whitney U test or Chi-squared test as appropriate. Analyses were undertaken using IBM SPSS statistical software (version 21).

RESULTS

Consecutive respiratory function traces were analysed. Eighteen were rejected: six infants were intubated immediately after birth (all the infants were less than 26 weeks of gestation), five infants could not be matched for gestational age, three infants had made a spontaneous breath prior to the first five inflations and four infants had poor quality traces. There were no significant differences in the demographics of the four groups (Table 1). At long inflation times, the expiratory tidal volumes ($p=0.004$) and the percentage leak ($p=0.02$) were greater at higher compared to lower pressures (Table 2). At short inflation times, the expiratory tidal volumes ($p<0.001$) were greater and the leak was less ($p<0.001$) at higher versus lower pressure. At lower pressures, the expiratory tidal volume was greater ($p<0.001$) and the leak lower ($p=0.026$) at a long versus a short inflation time. If, however, data from the 13 infants in whom inflations produced no measurable T_{Ve} were excluded, the significant differences disappeared (Figure 1). The 13 infants had a median leak of 54%, which was within the range of the other infants. At higher pressures and longer versus shorter inflation times, the percentage leak was greater ($p=0.024$) but there was no significant difference in the expiratory tidal volumes ($p=0.247$).

There were no significant differences in clinical outcomes between the three groups (Table 3).

DISCUSSION

We have demonstrated that higher inflation pressures, regardless of the inflation time, produced significantly higher expired tidal volumes. Face mask leak was high with prolonged inflation times, particularly at high inflation pressures and this may have affected the tidal volume delivered. The recommendation to use a prolonged inflation time is derived from a study assessing term born newborns who had been born following elective caesarean sections under general anaesthetic [9]. Infants born by elective caesarean section have fluid filled lungs with a high viscous resistance, hence the need for a sustained inflation to improve tidal volume. Prematurely born infants, many of whom are born following spontaneous vaginal delivery will already have had some lung fluid resorption, but are likely to have stiff lungs with a short time constant. Indeed, we have demonstrated that despite maintenance of the inflation time for a median of 0.89 seconds the median inflation flow time was 0.11 seconds with no significant correlation with inflation flow time and the inflation time [12]. Whether more prolonged inflations (> three seconds) are more effective requires further testing.

In this study, we found low expiratory tidal volumes and large leaks were common. On certain traces there was a high percentage of leak, but this reflects what can happen at resuscitations in the labour suite. We excluded active

inflations from the analysis as we wished to assess the effects of the combinations of different pressures and inflation times per se and it is not possible to determine the magnitude of the infant's contribution during active inflations. In a retrospective analysis, we demonstrated that higher pressures and longer inflation times were more likely to be associated with active inflations [14], whether this influences ventilation over the first minute has yet to be determined.

Our study has strengths and some limitations. During all the resuscitations a standard level of PEEP (4-5 cm H₂O) was used. We used a t-piece system to provide the PEEP as that system has been shown to provide more accurate and consistent PIP and PEEP compared to a self inflating bag with a PEEP valve [15]. At inflation pressures less than 20 cm H₂O, certain infants did not have measurable tidal volumes. Those infants had leaks within the range of the other infants. We did not, however, measure compliance and it may be that the infants had stiffer lungs and required elevation of the pressure after the first five inflations. The results of this study again emphasize that despite intensive training in the stressful situation which may be experienced in the labour suite, UK recommendations are not always followed. Indeed, the majority of the operators did not maintain the inflation time for two to three seconds (Table 2). This, however, gave us the opportunity to compare different combinations of inflation times and pressures. We do not report the results of a randomised trial, but a comparison of gestational age matched infants. Indeed, there were no significant differences in the demographics of the four groups (Table 1). Our study design enabled us to compare the efficacy of different combinations of

high and low pressures and short and long inflation times. We report the results of resuscitation during routine clinical care. We did not find any significant differences in clinical outcomes between the four groups. Those results, however, should be interpreted with caution as the numbers of infants in each group was relatively small.

CONCLUSIONS

Higher inflation pressures regardless of the length of the inflation time were associated with higher expiratory tidal volumes. Whether, however, a sustained inflation (≥ 15 seconds) with higher inflation pressures would have further efficacy needs testing in randomised trials.

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Conflict of interest: None to declare.

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FIGURE LEGEND

Figure 1: Plot of tidal volume against inflation times for infants who received the lower pressures. On the left hand side of the plot are data from the infants who received the shorter inflation times, some infants had no measurable tidal volumes. On the right hand side of the plot are data from infants who received the longer inflation times